

Summary Basis for Regulatory Action

Date: 1/28/2016

From: Brian Niland, Ph.D., Chair of the Review Committee

BLA/ STN#: 125585

Applicant Name: Bloodworks (formerly Puget Sound Blood Center)

Date of Submission: January 28, 2015

PDUFA Goal Date: January 28, 2016

Proprietary Name: None

Non-Proprietary name: HPC, Cord Blood

Indication: HPC (Hematopoietic Progenitor Cell), Cord Blood is an allogeneic cord blood hematopoietic progenitor cell therapy indicated for use in unrelated donor hematopoietic progenitor cell transplantation procedures in conjunction with an appropriate preparative regimen for hematopoietic and immunologic reconstitution in patients with disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment. The risk benefit assessment for an individual patient depends on the patient characteristics, including disease, stage, risk factors, and specific manifestations of the disease, on characteristics of the graft, and on other available treatments or types of hematopoietic progenitor cells.

Recommended Action: Approval

Signatory Authorities Action:

Offices Signatory Authority:

Celia Witten, PhD, MD, Office Director, Office of Cellular, Tissue, and Gene Therapies

☒ I concur with the summary review.

☐ I concur with the summary review and include a separate review to add further analysis.

☐ I do not concur with the summary review and include a separate review.

Mary Malarkey, Director, Office of Compliance and Biologics Quality

☒ I concur with the summary review.

☐ I concur with the summary review and include a separate review to add further analysis.

☐ I do not concur with the summary review and include a separate review.

Material Reviewed/ Consulted Specific Documentation Used in Developing the SBRA

Material Reviewed/ Consulted	Reviewer Name – Document(s) Date
CMC Review	January 27, 2016, Niland, Varadkar, Degheidy, Ghosh, Karandish
CBER Lot Release	January 26, 2016 Anderson
Facilities Review	January 28, 2016 Coats
Environmental Assessment	January 28 2016 Coats
Establishment Inspection	January 28, 2016 Coats
Nonclinical Pharmacology/Toxicology Review	November 19, 2015 Lu
Clinical and Statistical Joint Review	January 26, 2016 Lim, Luo
Advertising and Promotional Labeling Review	January 14, 2016 Nguyen
Division Director's Secondary CMC Review	January 27, 2016 Benton, Puri
Division Director's Secondary Clinical Review	January 7, 2016 Bryan

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1. Introduction

Biologics License Application (BLA) STN#125585 is for HPC, Cord Blood which is manufactured by Bloodworks, of Seattle, WA. Bloodworks HPC, Cord Blood, is an allogeneic cord blood hematopoietic progenitor cell therapy indicated for use in unrelated donor hematopoietic progenitor cell transplantation procedures in conjunction with an appropriate preparative regimen for hematopoietic and immunologic reconstitution in patients with disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment.

The risk-benefit assessment for an individual patient depends on the patient characteristics, including disease, stage, risk factors, and specific manifestations of the disease, on characteristics of the graft, and on other available treatments or types of hematopoietic progenitor cells.

This document summarizes the basis for the approval of Bloodworks HPC, Cord Blood. All findings identified during the review of the BLA have been adequately addressed. The review team recommends marketing approval of the product.

2. Background

HPC, Cord Blood is rich in hematopoietic progenitor cells, and has been used in the treatment of a variety of disorders, including hematologic malignancies, metabolic disorders, and immunodeficiencies.

Regulatory History

In an October 2009 Federal Register notice, FDA announced that manufacturers of cord blood will be required to have an approved BLA or IND in effect for unrelated cord blood shipped after October 20, 2011.

FDA developed and finalized guidance for industry entitled *Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution for Specified Indications* (October 2009). A new, updated final guidance of the same title was issued in March 2014. This guidance provides recommendations for the submission of a BLA for placental/umbilical cord blood.

On January 28, 2015, Bloodworks submitted a BLA to request licensure of HPC, Cord Blood. The applicant followed FDA guidance recommendations and cited data in the dockets (FDA-1997-N-0010 and FDA-2006-D-0157) as primary evidence of the efficacy and safety of HPC, Cord Blood. The applicant also submitted its own observational dataset to support the efficacy and safety of the product.

On November 2, 2015, the applicant submitted to FDA a request for a legal name change from Puget Sound Blood Center to Bloodworks. They were issued a new license number (U.S. License Number 2042) by letter on November 16, 2015, for their previously approved blood products. On December 1, 2015, the applicant submitted an updated Form FDA 356h to this BLA to document their name change to Bloodworks.

3. Chemistry Manufacturing and Controls (CMC)

a) Product Quality

Product Description

HPC, Cord Blood is manufactured by Bloodworks. The manufacture of HPC, Cord Blood by Bloodworks is consistent with recommendations made in the FDA licensure guidance.

Mothers who consent to donate their newborn's cord blood for public banking are screened and tested for communicable infectious diseases per regulations in 21 CFR 1271 Subpart C. HPC, Cord Blood is processed from cord blood collected from mothers who screen and test negative for the relevant infectious disease markers. A positive CMV result is allowed, and the CMV result will be reported to the transplant center when the lot of HPC, Cord Blood is selected. Cord blood units are obtained at seventeen collection sites in three states, and transported to the Bloodworks receiving and processing location (Seattle, WA) using validated and temperature-monitored shipping containers. HPC, Cord Blood is tested in multiple laboratories and maintained in a single, final storage location in their Seattle manufacturing site.

HPC, Cord Blood is processed by volume reduction and partial red cell and plasma depletion of collected cord blood using the (b) (4) system which is FDA cleared (b) (4). The volume of the final product is 25 ml and contains approximately 10% DMSO, 1% Dextran 40, (b) (4) hydroxyethyl starch, and (b) (4) citrate phosphate dextrose anticoagulant. The final product is tested for purity, identity, sterility, and potency. Each unit is frozen using a controlled rate freezing process (b) (4) freezer device) and then stored in liquid nitrogen ($\leq -150^{\circ}\text{C}$). The cryobag is placed and maintained inside a protective metal canister for freezing and storage in liquid nitrogen.

HPC, Cord Blood will have a 24 month dating period from the date of cryopreservation. There is a (b) (4)

HPC, Cord Blood is shipped frozen in special shipping containers (dry-shippers) designed to maintain a controlled environment and a very low temperature ($\leq -150^{\circ}\text{C}$). Shipping must occur within 5 days and temperature is electronically monitored and recorded for the entire transit time.

The procedures for thawing and washing have been validated. Directions for thawing are appended to the end of the prescribing information in the section “Instructions for Preparation for Infusion”, and will be included with each shipped unit of HPC, Cord Blood.

Manufacturing Controls

Process and product controls are in place to assure the quality of HPC, Cord Blood. There are specified time limits for all manufacturing process steps; cord blood is processed and frozen within 48 hours of collection. Lot release is based on a combination of in-process testing results as well as final product testing.

A summary of the product release tests performed on each lot of HPC, Cord Blood is shown below in Table 1. Infectious disease testing is performed on a maternal blood sample; hemoglobin analysis and ABO/Rh typing are performed on cord blood unit (b) (4) samples; sterility testing is performed on the processing (b) (4); and the rest of the testing is performed on (b) (4) cord blood samples. All product release tests must meet specifications for the product to be released into the search inventory. Confirmatory HLA typing is performed on an attached segment at the time of release for transplantation.

Table 1: Product Release acceptance criteria for HPC, Cord Blood

Product Characteristics	Testing Required	Tests Performed	Sample (Type and Timing)	Results of Product Testing
Safety	Infectious diseases	anti-HIV-1/2, HIV-1/2 RNA, anti-HCV, HCV RNA, anti-HBc, HBsAg, HBV DNA, anti-HTLV-I/II, anti-CMV, WNV RNA, Syphilis, and anti-T. cruzi (Chagas Disease)	Maternal peripheral blood obtained within 7 days of cord blood collection	All relevant communicable disease tests negative; CMV results are reported
	Sterility - Bacterial and fungal cultures	(b) (4)	(b) (4)	No growth
	Hemoglobin	(b) (4)	(b) (4)	No homozygous or double heterozygous hemoglobinopathy
Purity and Potency	Total nucleated cells (TNC)	(b) (4)	HPC, Cord Blood (pre-cryopreservation)	$\geq 5.0 \times 10^8$ TNC / unit HPC, Cord Blood
	Viable nucleated cells	(b) (4)		$\geq 85\%$ viable nucleated cells
	Viable CD34+ cells (flow cytometry)	(b) (4)		$\geq 1.25 \times 10^6$ viable CD34+ cells / unit HPC, Cord Blood
	(b) (4)	(b) (4)		(b) (4)
Identity	Human leukocyte antigen (HLA) Typing	(b) (4)	(b) (4)	Report
	Confirmatory HLA typing	(b) (4)	Attached segment of HPC, Cord Blood unit	Confirms initial typing
	Blood group and Rh type	ABO/Rh type	(b) (4)	(b) (4)

Manufacturing Risks

The greatest risks associated with the manufacture of the HPC, Cord Blood are 1) the risk of transmitting infectious diseases, 2) the risk of product contamination, particularly during collection of the cord blood and also during processing, and 3) the stability of the product during cryostorage or thawing. These risks are mitigated by various approaches.

To address infectious disease risks, medical records are reviewed for high-risk exclusions, and mothers of the newborn donors are also screened and tested for relevant communicable diseases according to 21 CFR 1271 regulations. Cord blood collection is performed in the delivery suites and the collection staff is trained to use aseptic technique and appropriate gowning, and collect one cord blood unit at a time.

Each collected cord blood unit is given a unique bar code ID number (ISBT128) which is both machine and manually readable. This bar code is associated with all test results (maternal and cord blood) as well as the matched patient data.

To address contamination risks, collection and processing personnel are trained appropriately. The processing methods have been validated to ensure aseptic processing. An automated functionally closed system (sterile single-use bag set/kit) is used in processing the collected cord blood. DMSO (b) (4)

Post-processing samples are tested for microbial contamination and must be negative.

To preserve cell potency, HPC, Cord Blood is frozen using a controlled rate freezing process and then stored in liquid nitrogen ($\leq -150^{\circ}\text{C}$). The HPC, Cord Blood is placed in an (b) (4) material “overwrap” bag before being placed in the metal canister for freezing.

The applicant provided data to validate the freezing and thawing procedures and to establish the product dating period. Based on the stability data submitted to the BLA, the current dating period for HPC, Cord Blood is 24 months.

b) CBER Lot Release

An exemption has been granted from CBER Lot Release testing, including no requirement for submission of product samples to CBER. The basis for this decision is the fact that each lot is a single HPC, Cord Blood unit that will treat a single patient. Lot release testing would negatively impact the often limited quantity of cells available to the patient, and failure of a single lot will have a minimal potential impact on public health.

c) Facilities review/inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facility involved in the manufacture of HPC, Cord Blood is listed in the table below. The activities performed and inspectional histories are noted in the table and are further described in the paragraph that follows.

Manufacturing Facilities Table for HPC Cord Blood

Name/address	FEI number	DUNS number	Inspection/waiver	Results/Justification
<i>HPC, Cord Blood</i> Drug Product Manufacturing, labeling and testing: Bloodworks (Formerly Puget Sound Blood Center) 921 Terry Ave. Seattle, WA 98104	3071347	092881085	Pre-license inspection	CBER July 2015 VAI

CBER conducted a pre-license inspection (PLI) of Puget Sound Blood Center and Program Cord Blood Services (PSBC) from July 13 – 17, 2015 for the manufacture of HPC ,Cord Blood. At the end of the inspection CBER issued a Form FDA 483 with four observations. The firm responded to the observations on July 31, 2015 and the corrective actions were reviewed and found to be adequate. All inspectional issues are considered to be satisfactorily resolved.

d) Container Closure System

HPC, Cord Blood is processed using a 510(k) cleared functionally-closed single use separation kit manufactured by (b) (4). The separation kits are composed of a proprietary separation chamber, tubing and final product/by-product bags. Integrity of the separation kit and final product bag was demonstrated through the execution of aseptic process simulation studies and acceptable sterility testing of the final product at the end of shelf life.

e) Environmental Assessment

Bloodworks requested a categorical exclusion from an environmental assessment pursuant to 21 CFR 25.31 (c), which applies to a biologic product containing substances that occur naturally in the environment when the introduction of the product does not alter significantly the concentration or distribution of the substances, their metabolites, or degradation products in the environment. The request for categorical exclusion is justified because the product meets the applicable exclusion criteria in 21 CFR Part 25, and there is no information indicating that extraordinary circumstances exist.

4. Nonclinical Pharmacology/Toxicology

No preclinical pharmacology/toxicology studies were conducted with HPC, Cord Blood manufactured by Bloodworks due to the minimal manipulation of the HPC, Cord Blood and the previous human experience with HPC, Cord Blood.

HPC, Cord Blood contains 10% DMSO, 1% Dextran 40, and (b) (4) hydroxyethyl starch; see Section 7 *Safety* regarding potential toxicities following exposure to this product.

5. Clinical Pharmacology

No studies of drug interactions have been performed with Bloodworks HPC, Cord Blood.

6. Clinical / Statistical

a) Clinical Program

This BLA proposes the use of Bloodworks HPC, Cord Blood in unrelated donor hematopoietic progenitor cell transplantation procedures in conjunction with an appropriate preparative regimen for hematopoietic and immunologic reconstitution in patients with disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment. The BLA submission includes data from clinical experience with Bloodworks HPC, Cord Blood and references data in the dockets FDA-1997-N-0010 (Legacy Docket number 97N-0497) and FDA-2006-D-0157 (Legacy Docket number 06D-0514). The clinical team also considered the available scientific literature and the results of the Cord Blood Transplantation (COBLT) study. The review team determined that the BLA submission was sufficient for assessment of the safety and efficacy of the Bloodworks HPC, Cord Blood.

Clinical efficacy review:

The efficacy of HPC, Cord Blood for hematopoietic reconstitution has been established by FDA analyses of the docket data as well as the COBLT study and other published observational studies. Assessment of hematopoietic reconstitution was based primarily on analyses of neutrophil and platelet recovery (see Table 2) of patients who received a suitable cord blood dose (i.e., a total nucleated cell dose $\geq 2.5 \times 10^7/\text{kg}$). Neutrophil recovery is defined as the time from transplantation to an absolute neutrophil count more than 500 per microliter. Platelet recovery is the time to a platelet count more than 20,000 per microliter. Erythrocyte recovery is the time to a reticulocyte count greater than 30,000 per microliter. The total nucleated cell dose and degree of HLA match were inversely associated with the time to neutrophil recovery in the docket data. Sixty-six percent (n=862) of the 1299 patients in the docket data who received a total nucleated cell dose $\geq 2.5 \times 10^7/\text{kg}$ underwent transplantation as treatment for hematologic malignancy.

Table 2 Hematopoietic Recovery for Patients Transplanted with Bloodworks HPC, Cord Blood, COBLT and Docket Data Total Nucleated Cell (TNC) Dose $\geq 2.5 \times 10^7/\text{kg}$

Data Source	Bloodworks HPC, Cord Blood Program	COBLT Study	Docket And Public Data
Design	Retrospective	Single-arm prospective	Retrospective
Number of Patients	N=Variable**	N=324	N=1299
Median age (range)	35 (<1-72) yrs	4.6 (0.07-52.2) yrs	7.0 (<1-65.7) yrs
Gender	59% male 41% female	59% male 41% female	57% male 43% female
Median TNC Dose (range) ($\times 10^7/\text{kg}$)	3.9 (2.5-42.3) ^β	6.7 (2.6-38.8)	6.4 (2.5-73.8)
Neutrophil recovery by Day 42 (95% CI)	82% (77% - 87%)	76% (71% - 81%)	77% (75% - 79%)
PLT recovery by Day 100 (20,000/ μl)	66% (60% - 72%)	57% (51% - 63%)	-
Platelet recovery by Day 100 (50,000/ μl)	50% (42% - 59%)	46% (39% - 51%)	45% (42% - 48%)
Erythrocyte Recovery at Day 100 (95% CI)	-	65% (58%-71%)	-
Median time to neutrophil recovery	21.5 days	27 days	25 days
Median time to platelet recovery (20,000/ μl)	46 days	90 days	-
Median time to platelet recovery (50,000/ μl)	53 days	113 days	122 days
Median time to Erythrocyte Recovery	-	64 days	-
Primary graft failure	17.2%	-	16.4%

** Sample size for median age = 468. N for gender= 468. Median TNC dose n = 194 (from units $\geq 2.5 \times 10^7$)
Neutrophil data n= 339. For $\geq 20\text{k}$ Platelet n= 328. N for $\geq 50\text{k}$ platelet = 267. N for primary graft
failure for patients who received a suitable graft = 203

^β Median TNC dose (all doses) = 3.2×10^7

The primary graft failure rate for patients receiving a TNC dose $\geq 2.5 \times 10^7/\text{kg}$ was 16.4% in the pooled docket dataset, and 17.2% in Bloodworks patients who received a suitable allograft. The clinical data, as illustrated in Table 2, provide evidence that transplantation of the Bloodworks HPC, Cord Blood results in hematopoietic and immunologic reconstitution as demonstrated by neutrophil, platelet, and erythrocyte recovery. Considering these data,

the review team concludes that this BLA provides substantial evidence that Bloodworks HPC, Cord Blood is effective for the proposed indication.

As illustrated in Table 2, certain outcomes of hematopoietic reconstitution may appear to be better for patients who received Bloodworks HPC, Cord Blood than for subjects in the COBLT study or for the patients in the overall pooled docket data. However, assessment of efficacy in the BLA review is based on voluntary data collection and data for many of the outcome parameters are missing in various degree. In addition, there is insufficient information in the various datasets about the nature of the diseases and their severity, and about the transplant preparative regimens. Due to the paucity of such information to inform comparisons between products, the data are insufficient to support a claim of superior effectiveness of Bloodworks HPC, Cord Blood over other HPC, Cord Blood products.

b) Pediatrics

Under PREA (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. This application does not trigger PREA.

c) Other Special Populations

Clinical experience with Bloodworks HPC, Cord Blood did not include sufficient numbers of patients aged 65 and older to determine whether they respond differently to Bloodworks HPC, Cord Blood than younger patients.

7. Safety

The safety review of HPC, Cord Blood was based on a review of submissions to the docket, the dataset for the COBLT Study, and published literature. The safety assessment of Bloodworks HPC, Cord Blood was based on the safety review of HPC, Cord Blood from various manufacturers, along with review of the applicant's BLA dataset that consists of patients who have received one or more units of Bloodworks-manufactured (b) (4). There was partial information in the Bloodworks dataset on 537 patients, and sufficient information on 212 patients to determine they received suitable allografts, defined as receiving a total nucleated cell dose $\geq 2.5 \times 10^7/\text{kg}$ and HLA match of 4/6 or more. The safety review focused on infusion reactions, deaths (Day-100 mortality), graft-versus-host disease, engraftment syndrome, donor cell leukemia, transmission of infection, and transmission of inheritable genetic disorders.

a) Infusion Reactions

The data described in Table 3 reflect exposure to 442 infusions of HPC, Cord Blood (from multiple cord blood banks) in patients treated using a total nucleated cell dose $> 2.5 \times 10^7/\text{kg}$

on a single-arm trial (COBLT Study). The population was 60% male, and the median age was 5 years (range 0.05-68 years), and included patients treated for hematologic malignancies, inherited metabolic disorders, primary immunodeficiencies, and bone marrow failure. Preparative regimens and graft-versus-host disease prophylaxis were not standardized. The most common infusion reactions were hypertension, vomiting, nausea, and bradycardia. Hypertension and any grades 3-4 infusion-related reactions occurred more frequently in patients receiving volumes greater than 150 milliliters and in pediatric patients. The rate of serious adverse cardiopulmonary reactions was 0.8%.

Table 3: Incidence of Infusion-Related Adverse Reactions Occurring in $\geq 1\%$ of Infusions (COBLT Study)

Adverse Reaction	Any Grade	Grade 3-4
Any reaction	65.4%	27.6%
Hypertension	48.0%	21.3%
Vomiting	14.5%	0.2%
Nausea	12.7%	5.7%
Sinus bradycardia	10.4%	0
Fever	5.2%	0.2%
Sinus tachycardia	4.5%	0.2%
Allergy	3.4%	0.2%
Hypotension	2.5%	0
Hemoglobinuria	2.1%	0
Hypoxia	2.0%	2.0%

Infusion reactions are defined as adverse events occurring within 24 hours after transplantation. Preparative regimens and graft-versus-host disease prophylaxis were not standardized. Bloodworks only received notice of those infusions where an adverse event report of Grade 3 or higher was submitted. Information on infusion reactions was available from voluntary reports for 212 infusions for patients who received Bloodworks HPC, Cord Blood at a total nucleated cell dose $\geq 2.5 \times 10^7/\text{kg}$; of these, 22 infusion reactions (10.4%) were reported to Bloodworks. The most frequent infusion reactions in Bloodworks HPC, Cord Blood data were hypertension (63.6%), nausea (27.3%) and chest pain (18.2%).

b) Adverse Reactions other than Infusion Reactions

For other adverse reactions (i.e., other than infusion reactions), the raw clinical data from the docket were pooled for 1299 patients (120 adult and 1179 pediatric) transplanted with HPC, Cord Blood (from multiple cord blood banks) with total nucleated cell dose $\geq 2.5 \times 10^7/\text{kg}$. Sixty-six percent (n=862) underwent transplantation as treatment for hematologic malignancy. The preparative regimens and graft-versus-host disease prophylaxis varied. The median total nucleated cell dose was 6.4 (range, 2.5 - 73.8) $\times 10^7/\text{kg}$. Limited data on other adverse reactions were also available for patients treated with Bloodworks HPC, Cord Blood.

- Deaths (Day-100 mortality)

For the 1299 patients in the pooled dataset, Day-100 mortality from all causes was 25%. Primary graft failure occurred in 16%. For the 212 patients with a suitable allograft in the Bloodworks HPC, Cord Blood dataset, Day-100 mortality from all causes was 22.6%. The incidences of the most common causes of death were infection (6.5%), primary disease (4.7%), organ failure (4.7%), and graft failure (2.3%).

- Graft-versus-Host Disease (GVHD)

For patients in the pooled docket dataset who received a TNC dose $\geq 2.5 \times 10^7/\text{kg}$, the incidence of grades 2-4 GVHD was 42%, and of grades 3-4 GVHD was 19%. For patients who received a suitable allograft of Bloodworks HPC, Cord Blood, 58% developed grades 1-4 acute GVHD, and 26.6% developed chronic GVHD.

- Engraftment Syndrome (ES)

The data in the docket do not address the risk of ES. In addition, the BLA does not provide any reports of ES associated with Bloodworks HPC, Cord Blood. However, ES occurred in 15% (11.7-18.0%) of the 364 patients in the COBLT study. Median time to onset of the event was 10 days after transplantation (range, 5-35 days). In literature reports, the incidence of ES varies from 30% to 78%.

- Donor Cell Leukemia, Transmission of Serious Infection, and Transmission of Rare Genetic Disorders

Data from published literature and from observational registries, institutional databases, and cord blood bank reviews reported to the docket revealed nine cases of donor cell leukemia, one case of transmission of infection, and one report of transplantation from a donor with an inheritable genetic disorder. The data are not sufficient to support reliable estimates of the incidences of these events. The BLA did not provide any reports of donor cell leukemia, transmission of serious infection, or transmission of rare genetic disorders associated with Bloodworks HPC, Cord Blood.

Due to differences in the size and quality of the datasets, the review team assessed the safety data from the pooled docket and other publically available data as the best indicator of the likely postmarketing performance of HPC, Cord Blood. Therefore, the package insert gives precedence to this pooled, publically available safety data over the Bloodworks HPC, Cord Blood safety data.

8. Advisory Committee Meeting

This application was not referred to an Advisory Committee because the product is not the first-in-class and the review committee did not identify novel concerns.

9. Other Relevant Regulatory Issues

Considering the extensive prior clinical experience with HPC, Cord Blood (from multiple cord blood banks), the review team determined that a pharmacovigilance plan was not necessary. In addition, review of the BLA did not identify any safety concerns that were not already known for this class of product. Therefore, the BLA review does not include a Pharmacovigilance Plan Review from the Office of Biostatistics and Epidemiology. However, to monitor the postmarketing safety of the product, the review team recommends a postmarketing safety outcomes monitoring and analysis plan, and expedited reporting of serious infusion reactions.

10. Labeling

The package insert (PI) originally submitted to the BLA and all subsequent amendments related to the label were reviewed by members of the BLA review team. Labeling for HPC, Cord Blood is primarily class labeling. Therefore, the labeling of Bloodworks HPC, Cord Blood follows the format of labeling of approved HPC, Cord Blood products.

Multiple discussions about the PI were held between review team members and the applicant. These discussions resulted in multiple rounds of revisions until final agreement was reached. The most significant discussions and changes related to clarifications needed in the Instructions for Preparation for Infusion.

The Advertising and Promotional Labeling Branch reviewed the package insert, patient labeling, and package and container labels. Changes to container and package labels were required in order to be in full compliance with regulations. After discussions with the applicant, the container and package labels were found to be acceptable.

The applicant will submit the label in Structured Product Labeling format after product licensure.

The proposed labeling provides adequate directions for the safe and effective use of HPC, Cord Blood in the indicated population.

11. Recommendations and Risk / Benefit Assessment

a) Recommended Regulatory Action

The review team recommends approval of Bloodworks HPC, Cord Blood as indicated for use in unrelated donor hematopoietic progenitor cell transplantation procedures in conjunction with an appropriate preparative regimen for hematopoietic and immunologic reconstitution in patients with disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment. The risk-benefit assessment for an individual patient depends on the patient characteristics, including disease, stage, risk factors, and specific manifestations of the disease, on characteristics of the graft, and on other available treatments or types of hematopoietic progenitor cells.

The recommended minimum dose is 2.5×10^7 nucleated cells/kg at cryopreservation.

b) Risk / Benefit Assessment

The benefit of Bloodworks HPC, Cord Blood is based on hematopoietic and immunologic reconstitution in patients with disorders of the hematopoietic system. Considering the substantial risks associated with Bloodworks HPC, Cord Blood, the risk-benefit assessment is highly individualized.

The quality, efficacy, and safety of this product have been thoroughly reviewed and have been determined to be acceptable for use of this product as indicated in the label.

c) Recommendation for Postmarketing Risk Management Activities

There was no safety issue identified that warrants a Risk Evaluation and Mitigation Strategy (REMS). Bloodworks HPC, Cord Blood is expected to have a favorable risk-benefit profile.

d) Recommendation for Postmarketing Activities

There are no safety issues that warrant postmarketing requirements or commitments.

The review team recommended, and the applicant agreed to do, the following:

1. Implement a safety outcomes monitoring and analysis plan. This plan will include a) maintenance of an observational database to include, for all Bloodworks HPC, Cord Blood units released, information including but not limited to, time to neutrophil recovery, graft failure, survival, cause of death, infusion reactions, and other adverse experiences, b) aggregate analyses of interval and cumulative adverse experience reports, and c) safety outcomes analyses of interval and cumulative data that address early mortality, graft failure-related mortality, graft failure, time to neutrophil recovery, infusion-related events, and other adverse experiences. Reports will include

a description of the population analyzed, results of the analyses, whether outcomes indicators were triggered and, if so, what actions were implemented as a result.

2. Submit a 15-day “alert report” for each serious infusion reaction associated with administration of Bloodworks HPC, Cord Blood.